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Journal of Advanced Research (2014) 5, 209–218

Cairo University

Journal of Advanced Research

ORIGINAL ARTICLE

Pentafluorophenylammonium triflate (PFPAT) catalyzed facile construction of substituted chromeno[2,3-*d*]pyrimidinone derivatives and their antimicrobial activity

Majid Ghashang [a], Syed Sheik Mansoor [b,*], Krishnamoorthy Aswin [b]

[a] *Faculty of Sciences, Najafabad Branch, Islamic Azad University, Najafabad, Esfahan, Iran*
[b] *Research Department of Chemistry, Bioactive Organic Molecule Synthetic Unit, C. Abdul Hakeem College, Melvisharam 632 509, Tamil Nadu, India*

ARTICLE INFO

Article history:
Received 25 December 2012
Received in revised form 27 February 2013
Accepted 12 March 2013
Available online 20 March 2013

Keywords:
Pentafluorophenylammonium triflate
Coumarin-3-carboxylic acid
Antimicrobial activity
Chromeno[2,3-d]pyrimidinones
2-Amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate

ABSTRACT

A new, simple thermally efficient and solvent-free condensation of 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives with coumarin-3-carboxylic acid employing pentafluorophenylammonium triflate (PFPAT) as an inexpensive organocatalyst for the synthesis of a series of ethyl 4,5-dihydro 7-methyl-2-(2-oxo-2*H*-chromen-3-yl)-4-oxo-5-aryl-3*H*-chromeno[2,3-*d*]pyrimidine-6-carboxylate derivatives is described. This method has the advantages of high yields, a cleaner reaction, simple methodology, short reaction times, easy workup, and greener conditions. All the compounds were evaluated for their *in vitro* antimicrobial activity against different bacterial and fungal strains.

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Introduction

Coumarins (2-oxo-2*H*-chromene) are the family of lactones containing benzopyran skeletal framework. Coumarin derivatives have been established as well-known naturally occurring oxygen-heterocyclic compounds isolated from various plants which occupy a special role in nature [1]. The plant extracts containing coumarin-related heterocycles are employed as herbal remedies in traditional systems of medicine. They belong to

* Corresponding author. Tel.: +91 9944 093020; fax: +91 4172 266487.
E-mail address: smansoors2000@yahoo.co.in (S.S. Mansoor).
Peer review under responsibility of Cairo University.

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http://dx.doi.org/10.1016/j.jare.2013.03.003

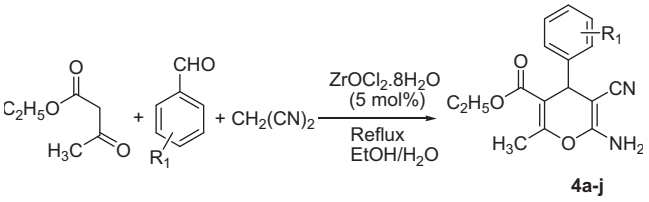
the flavonoid class of plant secondary metabolite. Coumarin derivatives constitute an important class of heterocyclic compounds that have attracted significant attention in recent years [2,3]. They have attracted intense interest because of their diverse pharmacological properties. Cancer, a diverse group of diseases characterized by uncontrolled growth of abnormal cells, is a major worldwide problem. It is a fatal disease standing next to the cardiovascular disease in terms of morbidity and mortality. A series of coumarin–chalcone hybrids have been synthesized and evaluated for their *in vitro* cytotoxicity against a panel of four human cancer cell lines and normal fibroblasts (NIH3T3) [4]. Tuberculosis (TB) is a common and often deadly infectious disease caused by various strains of mycobacterium, usually *Mycobacterium tuberculosis*. Tuberculosis has been considered to be a disease of poverty for many years with quite rare occurrence in the developed countries. A new series of 4-(3-coumarinyl)-3-benzyl-4-thiazolin-2-one benzylidenehydrazones were synthesized, and they were evaluated for anti-tuberculosis activity against *M. tuberculosis* H37Rv in BACTEC 12B medium using the BACTEC 460 radiometric system [5]. Coumarin derivatives also used as anti-HIV [6], antioxidant [7], dyslipidemic [8], anti-inflammatory agents [9], and antimicrobial agents [10].

In view of the pharmaceutical importance of heterocyclic compounds containing coumarin moiety, many methods have been developed. Coumarin derivatives are synthesized using different catalysts like nano-crystalline ZnO [11], heteropoly acids [12] and tetrabutylammonium bromide [13]. Recently, chromeno pyrimidinone derivatives [14] and quinoxaline derivatives containing the coumarin moiety [15] are reported. Various chromeno pyrimidinones are prepared under solvent-free condition at 120 °C in the presence of 10 mol% of ionic liquid [14].

Although these methods are quite satisfactory, many of them employ considerable amounts of hazardous organic solvents, which are not environmentally friendly, for carrying out the reactions and/or for extraction and purification (column chromatography). Furthermore, these methods are not suitable in terms of the recent trends in process chemistry, because of the use of metallic catalysts. Therefore, a method using a nonmetallic catalyst is desirable. Organo-catalysts have gained interesting attraction in recent years due to economic and environmental considerations. These catalysts are generally inexpensive and easily available. They can conveniently be handled and removed from the reaction mixture, thus making the experimental procedure simple and eco-friendly. The leading contenders for environmentally acceptable processes are supported reagents.

PFPAT as an efficient organo-catalyst was applied in various transformations. From the literatures, it was found that PFPAT is a useful catalyst for multi-component reactions (MCRs) [16–22], since it is low toxic catalyst, air and water compatible and has remarkable ability to suppress side reactions in acid-sensitive substrates.

Recently, Funatomi et al. reported the application of pentafluorophenylammonium triflate ($C_6F_5NH_3OTf$; PFPAT) as a novel heterogeneous catalyst in organic transformation such as esterification of carboxylic acids with alcohols [16], C-acylations of enol silyl ethers or ketene silyl (thio)acetals with acid chlorides [17] and Mukaiyama aldol and Mannich reactions using ketene silyl acetals with ketones and oxime ethers [18]. Further, PFPAT also used as the catalyst for acylation of alcohols, phenols, and amines [19], one-pot condensation of β-naphthol, aldehydes and cyclic 1,3-dicarbonyl compounds [20], synthesis of xanthenes derivatives [21], and Biginelli reaction [22]. However, to the best of our knowledge, there are no examples on the use of PFPAT as catalyst for the synthesis of ethyl-4,5-dihydro 7-methyl-2-(2-oxo-2*H*-chromen-3-yl)-4-oxo-5-aryl-3*H*-chromeno[2,3-d]pyrimidine-6-carboxylate derivatives.



Scheme 1 2-Amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives.

Recently, we have reported the synthesis of biologically active heterocyclic molecules, such as 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives [23], polyhydroquinoline derivatives [24], 2-amino-6-(2-oxo-2*H*chromen-3-yl)-4-arylnicotinonitrile derivatives [25], and 2-arylbenzothiazole derivatives [26] by multi-component reactions. In continuation of our research on the development of environmentally friendly procedures, we now describe the synthesis of ethyl-4,5-dihydro 7-methyl-2-(2-oxo-2*H*-chromen-3-yl)-4-oxo-5-aryl-3*H*-chromeno[2,3-*d*]pyrimidine-6-carboxylates using PFPAT as an efficient novel organocatalyst. These compounds were synthesized using 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylates (Scheme 1).

Experimental

Apparatus and analysis

Chemicals were purchased from Merck, Fluka, and Aldrich Chemical Companies. All yields refer to isolated products unless otherwise stated. ^{1}H NMR (500 M*Hz*) and ^{13}C NMR (125 M*Hz*) spectra were obtained using Bruker DRX-500 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr disks on Shimadzu spectrometer. Mass spectra were determined on a Varion – Saturn 2000 GC/MS instrument. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer flowchart.

Preparation of the catalyst (PFPAT)

To a solution of 2,3,4,5,6-pentafluoroaniline (25 mmol) in toluene (25 mL), CF_3SO_3H (25 mmol) was added at 0–5 °C. The reaction mixture was stirred at the same temperature for 30 min. After this time, the solvent was evaporated *in vacuo*, and the crude product was collected and washed with hexane to give the pure catalyst in 92% yield [16].

General procedure to synthesis of 2-amino-3-cyano-6-methyl-4-phenyl-4H-pyran-5-ethylcarboxylate derivatives using $ZrOCl_2{\cdot}8H_2O$ (5 mol%) as catalyst

A mixture of ethyl acetoacetate (1 mmol), aldehydes (1 mmol), malononitrile (1 mmol), and catalyst $ZrOCl_2{\cdot}8H_2O$ (5 mol%)

in 5 mL of EtOH/H_2O[50/50(v/v)] were refluxed for appropriated time. After the TLC indicates the disappearance of starting materials, the reaction was cooled to room temperature, ethanol (20 mL) was added, and the insoluble material was filtered to separate the catalyst. The filtrate was concentrated under vacuum, and the crude residue was purified by recrystallization. 2-Amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate was obtained as crystals. The recovered catalyst can be washed consequently with diluted acid solution, water, and then acetone. After drying, it can be reused without noticeable loss of reactivity. The products were identified by IR, ^{1}H NMR, ^{13}C NMR, mass, elemental analysis, and melting points.

Spectral data for the selected synthesized compounds

*2-Amino-3-cyano-6-methyl-4-(4-N,N-dimethylaminophenyl)-4H-pyran-5-ethylcarboxylate (**4d**)*

(KBr, cm^{-1}): 3413, 3342, 3214, 2217, 1662, 1638, 1484, 1203, 785; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.20 (t, J = 7.2 *Hz*, 3H, CH_3CH_2), 2.66 (s, 6H, $N(CH_3)_2$), 2.28 (s, 3H, CH_3), 4.11 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.94 (s, 1H, CH), 5.17 (s, 2H, NH_2), 7.11 (d, J = 7.2 *Hz*, 2H, ArH), 7.34 (d, J = 7.2 *Hz*, 2H ArH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 15.1, 19.2, 39.8, 57.4, 59.8, 105.8, 120.3, 125.2, 128.3, 129.1, 131.1, 144.8, 147.1, 166.5 ppm; MS (ESI): m/z 328 $(M+H)^+$. Anal. Calcd. for $C_{18}H_{21}N_3O_3$ (%): C, 66.05; H, 6.42; N, 12.84. Found: C, 66.00; H, 6.41; N, 12.85.

*2-Amino-3-cyano-6-methyl-4-(4-fluorophenyl)-4H-pyran-5-ethylcarboxylate (**4f**)*

IR (KBr, cm^{-1}): 3428, 3329, 3205, 2216, 1667, 1636, 1483, 1219, 793. ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.13 (t, J = 7.0 *Hz*, 3H, CH_3CH_2), 2.26 (s, 3H, CH_3), 4.06 (q, J = 7.0 *Hz*, 2H, CH_3CH_2), 4.90 (s, 1H, CH), 5.21 (s, 2H, NH_2), 7.10 (d, J = 7.4 *Hz*, 2H, ArH), 7.32 (d, J = 7.4 *Hz*, 2H ArH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 14.5, 19.6, 39.4, 58.0, 60.4, 105.3, 120.3, 125.0, 129.1, 131.1, 144.7, 146.7, 167.5 ppm; MS (ESI): m/z 303 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}FN_2O_3$ (%): C, 63.57; H, 4.96; N, 9.27. Found: C, 63.50; H, 4.95; N, 9.28.

*2-Amino-3-cyano-6-methyl-4-(4-methoxyphenyl)-4H-pyran-5-ethylcarboxylate (**4g**)*

IR (KBr, cm^{-1}): 3429, 3337, 3219, 2220, 1675, 1644, 1488, 1219, 779. ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.16 (t, J = 7.4 *Hz*, 3H, CH_3CH_2), 2.24 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 4.17 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.87 (s, 1H, CH), 5.15 (s, 2H, NH_2), 7.07 (d, J = 7.2 *Hz*, 2H, ArH), 7.34 (d, J = 7.2 *Hz*, 2H ArH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 14.9, 19.8, 40.6, 58.6, 60.6, 106.3, 119.9, 125.7, 128.4, 129.2, 131.2, 144.8, 147.3, 167.6 ppm; MS (ESI): m/z 315 $(M+H)^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_4$ (%): C, 64.97; H, 5.73; N, 8.92. Found: C, 64.90; H, 5.70; N, 8.91.

*2-Amino-3-cyano-6-methyl-4-(4-nitrophenyl)-4H-pyran-5-ethylcarboxylate (**4h**)*

IR (KBr, cm^{-1}): 3430, 3338, 3209, 2202, 1668, 1644, 1489, 1203, 774. ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.19 (t, J = 7.4 *Hz*, 3H, CH_3CH_2), 2.31 (s, 3H, CH_3), 4.14 (q, J = 7.3 *Hz*, 2H, CH_3CH_2), 4.92 (s, 1H, CH), 5.07 (s, 2H, NH_2), 7.15 (d, J = 7.4 *Hz*, 2H, ArH), 7.44 (d, J = 7.4 *Hz*, 2H ArH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 15.2, 20.2, 39.3, 58.3, 59.7, 105.7, 119.3, 125.6, 128.1, 129.0, 131.0, 144.1, 147.4, 167.0 ppm; MS (ESI): m/z 330 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}N_3O_5$ (%): C, 58.35; H, 4.56; N, 12.76. Found: C, 58.30; H, 4.53; N, 12.75.

General procedure for the synthesis of ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-phenyl-3H-pyrano[2,3-d]pyrimidine-6-carboxylate by PFPAT

A mixture of 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate **4a–j** (1 mmol), coumarin-3-carboxylic acid (1 mmol) and PFPAT (5 mol%) were heated at 80 °C for about 5.5–7.0 h (Scheme 2). After completion of the reaction as indicated by TLC, 2 mL of water was added and stirred at room temperature for 20 min. The precipitated product was filtered, washed with water, dried and purified over column chromatography using silica gel (230–400 mesh) with *n*-hexane and ethyl acetate (8:2) as eluent. The aqueous layer containing catalyst was recovered, washed with acetone, dried and reused for subsequent reactions without loss in its activity and product yield.

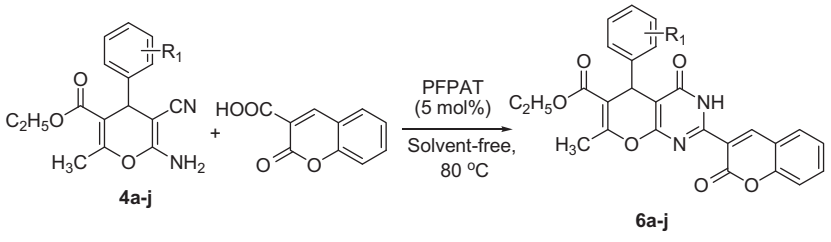
Recycling and reusing of the catalyst

The catalyst is soluble in water and could therefore be recycled as the filtrate. The catalyst was recovered by evaporation of the water, washed with hexane, dried at 50 °C under vacuum for 1 h, and reused in another reaction without appreciable reduction in the catalytic activity.

*Spectral data for the synthesized compounds (**6a–j**)*

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-phenyl-3H-pyrano[2,3-d] pyrimidine-6-carboxylate (**6a**)*

IR (KBr, cm^{-1}): 3311, 1714, 1677, 1638, 1600, 1208; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.18 (t, J = 7.4 *Hz*, 3H, CH_3CH_2), 2.22 (s, 3H, CH_3), 4.12 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.53 (s, 1H,



Scheme 2 Ethyl 4,5-dihydro 7-methyl-2-(2-oxo-2*H*-chromen-3-yl)-4-oxo-5-aryl-3*H*-chromeno[2,3-*d*]pyrimidine-6-carboxylate derivatives.

CH), 7.01–7.41 (m, 5H, ArH), 7.75–7.92 (m, 4H, ArH), 8.66 (s, 1H, Coumarin H), 9.07 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 16.4, 20.1, 26.4, 36.0, 37.4, 100.7, 113.5, 116.1, 118.0, 118.7, 121.3, 124.5, 126.4, 127.0, 129.3, 130.8, 134.0, 136.8, 153.0, 154.2, 157.0, 163.7, 170.4 ppm; MS(ESI): *m*/*z* 456 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{20}N_2O_6$: C, 68.42; H, 4.38; N, 6.14%. Found: C, 68.31; H, 4.33; N, 6.14%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(3-hydroxyphenyl)-3H-pyrano[2,3-d pyrimidine-6-carboxylate (**6b**)*

IR (KBr, cm^{-1}): 3362, 3308, 1712, 1675, 1640, 1609, 1212; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.10 (t, J = 7.2 *Hz*, 3H, CH_3CH_2), 2.18 (s, 3H, CH_3), 4.22 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.58 (s, 1H, CH), 7.09–7.49 (m, 4H, ArH), 7.71–7.90 (m, 4H, ArH), 8.70 (s, 1H, Coumarin H), 9.01 (s, 1H, NH), 9.66 (s, 1H, OH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 15.9, 20.2, 26.3, 36.4, 37.3, 100.6, 114.0, 116.4, 117.7, 118.8, 121.0, 124.3, 126.2, 127.2, 129.4, 130.4, 134.5, 136.8, 153.2, 154.5, 156.9, 163.6, 170.3 ppm; MS(ESI): *m*/*z* 473 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{20}N_2O_7$: C, 66.10; H, 4.24; N, 5.93%. Found: C, 66.01; H, 4.20; N, 5.90%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(3-nitrophenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6c**)*

IR (KBr, cm^{-1}): 3296, 1720, 1680, 1644, 1611, 1216; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.09 (t, J = 7.0 *Hz*, 3H, CH_3CH_2), 2.26 (s, 3H, CH_3), 4.26 (q, J = 7.0 *Hz*, 2H, CH_3CH_2), 4.44 (s, 1H, CH), 7.03–7.33 (m, 4H, ArH), 7.68–7.88 (m, 4H, ArH), 8.80 (s, 1H, Coumarin H), 9.05 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 16.2, 20.0, 26.7, 36.1, 37.1, 100.2, 113.7, 115.7, 117.6, 119.0, 121.4, 124.4, 126.7, 127.5, 128.6, 129.4, 130.6, 134.6, 136.8, 153.3, 154.5, 156.8, 162.9, 170.1 ppm; MS(ESI): *m*/*z* 502 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{19}N_3O_8$: C, 62.27; H, 3.79; N, 8.38%. Found: C, 62.22; H, 3.74; N, 8.35%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(N,N-dimethylaminophenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6d**)*

IR (KBr, cm^{-1}): 3304, 1704, 1688, 1633, 1604, 1200; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.12 (t, J = 7.2 *Hz*, 3H, CH_3CH_2), 2.27 (s, 3H, CH_3), 2.74 (s, 6H, $N(CH_3)_2$), 4.19 (q, J = 7.4 *Hz*, 2H, CH_3CH_2), 4.39 (s, 1H, CH), 7.08–7.17 (m, 2H, ArH), 7.34–7.48 (m, 2H, ArH), 7.74–7.82 (m, 4H, ArH), 8.77 (s, 1H, Coumarin H), 9.24 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 15.5, 20.3, 26.5, 36.5, 37.3, 46.5, 100.4, 113.9, 116.0, 118.1, 118.8, 122.0, 124.6, 126.3, 127.7, 129.5, 130.1, 134.3, 136.5, 153.0, 154.3, 156.7, 163.0, 170.2 ppm; MS(ESI): *m*/*z* 500 $(M+H)^+$; Anal. Calcd. for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.01; N, 8.42%. Found: C, 67.35; H, 5.00; N, 8.37%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(4-chlorophenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6e**)*

IR (KBr, cm^{-1}): 3294, 1716, 1677, 1640, 1609, 1206; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.16 (t, J = 7.1 *Hz*, 3H, CH_3CH_2), 2.19 (s, 3H, CH_3), 4.14 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.53 (s, 1H, CH), 7.11–7.24 (m, 2H, ArH), 7.42–7.52 (m, 2H, ArH), 7.76–7.96 (m, 4H, ArH), 8.75 (s, 1H, Coumarin H), 9.12 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 16.6, 20.7, 26.7, 35.9, 36.8, 101.0, 114.2, 116.2, 117.5, 119.1, 121.2, 124.8, 126.0, 127.5, 129.0, 130.1, 134.7, 136.9, 153.6, 154.2, 156.9, 162.7, 170.4 ppm; MS(ESI): *m*/*z* 491 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{19}ClN_2O_6$: C, 63.61; H, 3.87; N, 5.71%. Found: C, 63.58; H, 3.86; N, 5.73%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(4-fluorophenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6f**)*

IR (KBr, cm^{-1}): 3314, 1722, 1682, 1646, 1616, 1214; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.19 (t, J = 7.2 *Hz*, 3H, CH_3CH_2), 2.20 (s, 3H, CH_3), 4.17 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.55 (s, 1H, CH), 7.07–7.16 (m, 2H, ArH), 7.46–7.57 (m, 2H, ArH), 7.66–7.74 (m, 4H, ArH), 8.88 (s, 1H, Coumarin H), 9.10 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 15.9, 20.0, 26.4, 35.8, 36.7, 101.2, 113.9, 116.4, 117.7, 118.6, 121.5, 124.0, 125.9, 127.8, 129.4, 130.1, 133.9, 136.5, 153.4, 154.6, 157.2, 163.5, 170.3 ppm; MS(ESI): *m*/*z* 475 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{19}FN_2O_6$: C, 65.82; H, 4.01; N, 5.91%. Found: C, 65.80; H, 4.00; N, 5.90%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(4-methoxyphenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6g**)*

IR (KBr, cm^{-1}): 3310, 1711, 1668, 1652, 1603, 1205; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.08 (t, J = 7.2 *Hz*, 3H, CH_3CH_2), 2.27 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 4.10 (q, J = 7.1 *Hz*, 2H, CH_3CH_2), 4.35 (s, 1H, CH), 7.12–7.30 (m, 2H, ArH), 7.43–7.56 (m, 2H, ArH), 7.70–7.82 (m, 4H, ArH), 8.65 (s, 1H, Coumarin H), 9.06 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 16.1, 20.1, 26.4, 36.1, 37.4, 100.5, 113.8, 115.8, 117.6, 118.7, 121.2, 124.2, 126.1, 127.3, 129.2, 130.1, 134.4, 136.4, 153.7, 154.8, 157.3, 163.0, 170.2 ppm; MS(ESI): *m*/*z* 487 $(M+H)^+$; Anal. Calcd. for $C_{27}H_{22}N_2O_7$: C, 66.67; H, 4.53; N, 5.76%. Found: C, 65.70; H, 4.50; N, 5.75%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(4-nitrophenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6h**)*

IR (KBr, cm^{-1}): 3299, 1709, 1671, 1647, 1600, 1210; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.13 (t, J = 7.2 *Hz*, 3H, CH_3CH_2), 2.20 (s, 3H, CH_3), 4.20 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.30 (s, 1H, CH), 7.00–7.15 (m, 2H, ArH), 7.40–7.52 (m, 2H, ArH), 7.69–7.81 (m, 4H, ArH), 8.58 (s, 1H, Coumarin H), 9.21 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 16.7, 20.6, 26.6, 36.4, 37.6, 100.7, 113.3, 116.1, 118.0, 118.5, 121.4, 124.3, 125.8, 127.0, 129.4, 130.1, 134.0, 136.2, 153.3, 154.3, 156.7, 162.6, 170.6 ppm; MS(ESI): *m*/*z* 502 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{19}N_3O_8$: C, 62.27; H, 3.79; N, 8.38%. Found: C, 62.29; H, 3.79; N, 8.36%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(4-bromophenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6i**)*

IR (KBr, cm^{-1}): 3292, 1714, 1675, 1644, 1611, 1208; ^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 1.12 (t, J = 7.1 *Hz*, 3H, CH_3CH_2), 2.16 (s, 3H, CH_3), 4.16 (q, J = 7.2 *Hz*, 2H, CH_3CH_2), 4.56 (s, 1H, CH), 7.16–7.26 (m, 2H, ArH), 7.46–7.58 (m, 2H, ArH), 7.72–7.90 (m, 4H, ArH), 8.78 (s, 1H, Coumarin H), 9.09 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 16.5, 20.5, 26.5, 35.7, 36.6, 101.1, 114.4, 116.4, 117.4, 119.4, 121.6, 124.6, 126.0,

127.3, 129.2, 130.3, 134.5, 136.7, 153.7, 154.5, 156.7, 162.9, 170.7 ppm; MS(ESI): *m*/*z* 535.9 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{19}BrN_2O_6$: C, 58.32; H, 3.55; N, 5.23%. Found: C, 58.28; H, 3.50; N, 5.21%.

*Ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2H-chromen-3-yl)-5-(4-methylphenyl)-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (**6j**)*

IR (KBr, cm^{-1}): 3313, 1714, 1669, 1655, 1603, 1208; ^1H NMR (500 M*Hz*, $CDCl_3$) δ: 1.09 (t, J = 7.2 *Hz*, 3H, CH_3CH_2), 2.22 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.14 (q, J = 7.1 *Hz*, 2H, CH_3CH_2), 4.38 (s, 1H, CH), 7.18–7.35 (m, 2H, ArH), 7.45–7.58 (m, 2H, ArH), 7.77–7.88 (m, 4H, ArH), 8.69 (s, 1H, Coumarin H), 9.14 (s, 1H, NH) ppm; ^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 16.3, 20.3, 26.6, 27.3, 36.3, 37.8, 100.7, 113.4, 115.4, 117.9, 118.8, 124.4, 126.2, 127.0, 129.5, 130.4, 134.6, 137.0, 154.0, 155.9, 157.5, 163.3, 170.5 ppm; MS(ESI): *m*/*z* 471 $(M+H)^+$; Anal. Calcd. for $C_{27}H_{22}N_2O_6$: C, 68.93; H, 4.68; N, 5.95%. Found: C, 68.88; H, 4.65; N, 5.94%.

Results and discussion

The synthetic pathway of the title compounds was achieved *via* 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylates intermediates (**4a**–**j**). Considering the broad spectrum of biological activities of 4*H*-pyrans, synthetic chemists have developed numerous protocols for their syntheses including two-step as well as one-pot three component synthesis, catalyzed by Baker's yeast [27], MgO [28], hexadecyldimethylbenzyl ammonium bromide (HDMBAB) [29], phenylboronic acid [30], 2,2,2-trifluoroethanol [31], and silica gel-supported polyphosphoric acid (PPA–SiO_2) [32]. However, these methods often suffer from one or the other kind of drawbacks and most of them give moderate yields even after prolonged reaction time. This has clearly indicated that there is still scope to develop an efficient and eco-sustainable method for the synthesis of 4*H*-pyrans. The intermediates were obtained by the three component condensation of ethyl acetoacetate, aldehydes with malononitrile using $ZrOCl_2{\cdot}8H_2O$ as catalyst in aqueous ethanol.

In order to optimize the conditions, we studied the reaction of ethyl acetoacetate, benzaldehyde with malononitrile and $ZrOCl_2{\cdot}8H_2O$ (5 mol%) as a simple model reaction in various conditions. The reaction was performed in various solvents to identify the best solvent condition. A range of solvents like CH_3CN, CH_3Cl, EtOH, and H_2O were examined at reflux condition (Table 1, Enries 1–4). The reaction without any solvent at reflux was not very successful (Table 1, Entry 5). The model reaction was studied at various mixtures of EtOH/H_2O solvent. The EtOH/H_2O[50/50(v/v)] is proven to be the most suitable solvent for this condensation in terms of yield and reaction time (Table 1, Entry 7). We have studied the amount of $ZrOCl_2{\cdot}8H_2O$ required for the reaction. It was found that when decreasing the amount of the catalyst from 5 mol% to 3 mol%, the yield decreased from 95% to 77% (Table 1, Entry 9). When increasing the amount of the catalyst from 5 mol% to 10 mol%, there is no change in the yield (Table 1, Entry 10). The use of 5 mol% of $ZrOCl_2{\cdot}8H_2O$ maintaining the yield at 95%, so this amount is sufficient to promote the reaction. In the presence of more than this amount of the catalyst, neither the yield nor the reaction time was improved (Table 1, Entry 10). Encouraged by this successful three component reaction, synthesis of diverse 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives **4a**–**j** was undertaken. The aromatic aldehydes bearing electron-withdrawing and electron donating groups were found to be equally effective to produce 2-amino-4*H*-pyrans **4a**–**j** in very good yields (Table 2).

After the synthesis of 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives, we have synthesized Ethyl 4,5-dihydro 7-methyl-2-(2-oxo-2*H*-chromen-3-yl)-4-oxo-5-aryl-3*H*-chromeno[2,3-*d*]pyrimidine-6-carboxylate derivatives. Initially, the reaction between compound 4a and coumarin-3-carboxylic acid was carried out under neat conditions at 80 °C without and with different acid catalyst (phenylboronic acid, bismuth nitrate, silica perchloric acid, sulfamic acid, PFPAT each 5 mol%) and observed maximum yield with PFPAT (Table 3).

The solvents played an important role in the synthesis of chromeno pyrimidine derivatives. Various reaction media were screened (1,4-dioxane, ethanol, acetonitrile, THF, methanol, and *t*-BuOH) using the model reaction (Table 4, Entries 1–6). It was found that the best results were obtained with 5 mol% of PFPAT under solvent-free condition (Table 4, Entry 7). The reaction was completed in 6 h, and the expected product was obtained in 89% yield.

At these optimize conditions (solvent-free, 80 °C, 5 mol% of PFPAT), we synthesized various chromeno pyrimidinones **6a**–**j** (Table 5). After completion of the reaction, the catalyst was recovered by evaporating the aqueous layer, washed with

Table 1 Optimization of the reaction conditions on the synthesis of **4a**: Effect of solvent and catalyst amount.[a]

Entry	Solvent	Amount of catalyst (mol%)	Time (h)	Yield (%)[b]
1	CH_3CN	5	3	41
2	$CHCl_3$	5	3	62
3	H_2O	5	3	72
4	EtOH	5	3	68
5	None	5	3	31
6	EtOH/H_2O[30/70(v/v)]	5	1.5	78
7	EtOH/H_2O[50/50(v/v)]	5	1.5	95
8	EtOH/H_2O[70/30(v/v)]	5	1.5	80
9	EtOH/H_2O[50/50(v/v)]	3	1.5	77
10	EtOH/H_2O[50/50(v/v)]	10	1.5	96

[a] Reaction conditions: ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) at reflux.
[b] Isolated yield.

Table 2 Preparation of various 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives.[a]

Entry	R1	Product	Time (h)	Yield (%)[b]	Mp (°C)	
					Found	Reported
1	H	**4a**	1.5	95	193–195	195–196 [28]
2	3-OH	**4b**	1.5	93	162–164	161–162 [28]
3	3-NO_2	**4c**	1.0	90	182–184	182–183 [28]
4	4-$N(CH_3)_2$	**4d**	2.0	88	180–182	–
5	4-Cl	**4e**	1.5	87	170–172	172–174 [28]
6	4-F	**4f**	1.5	91	186–188	–
7	4-OCH_3	**4g**	2.0	87	141–143	142–144 [28]
8	4-NO_2	**4h**	2.5	89	182–184	180–182 [28]
9	4-Br	**4i**	1.5	90	172–174	–
10	4-CH_3	**4j**	2.0	86	178–180	177–179 [28]

[a] Reaction conditions: ethyl acetoacetate (1 mmol), aldehyde (1 mmol), and malononitrile (1 mmol) in the presence of $ZrOCl_2{\cdot}8H_2O$ (5 mol%) in $EtOH/H_2O$[50/50(v/v)] at reflux.
[b] Isolated yield.

Table 3 Preparation of ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate: effect of catalyst.[a]

Entry	Catalyst	Amount of catalyst (mol%)	Time (h)	Yield (%)[b]
1	Phenylboronic acid	5	8	55
2	Bismuth nitrate	5	8	62
3	Silica perchloric acid	5	8	72
4	Sulfamic acid	5	8	68
5	PFPAT	5	6	89
6	None	0	8	Trace
7	PFPAT	10	6	89
8	PFPAT	3	6	84
9	PFPAT	2	6	75

[a] Reaction conditions: **4a** (1 mmol) and coumarin-3-carboxylic acid (1 mmol) at 80 °C.
[b] Isolated yield.

acetone, dried and reused for subsequent reactions without significant loss in its activity. The catalyst was recycled for four runs without loss of its activity (Table 5, Entry 1). All the synthesized compounds were confirmed by their analytical and spectroscopic data.

To explain the formation of **6a** as a model *via* the condensation reaction, we have proposed a plausible reaction mechanism, which is illustrated in Scheme 3. Firstly, the protonation of coumarin-3-carboxylic acid by PFPAT as a Brønsted acid was occurred to form a cation intermediate (**a**). In continue, the formation of (**b**) resulting from the amidation of (**a**) with **4a** was established. In the next step, the protonation of nitrile group of intermediate (**b**) following by a cyclo-addition reaction was occurred to form the intermediate (**c**). In continue the addition reaction of pentafluorophenyl amine (PFPA) followed by ring-opening of the (**c**) to the intermediate (**d**) and (**e**) followed by ring closure of intermediate (**e**) results in the formation of intermediate (**f**) that convert to the (**6a**) as product by the de-protonation reaction. Interestingly, the formation of compound **6a**, obtained from the condensation of coumarin-3-carboxylic acid with **4a**, confirms the mechanism of the reaction which was rarely described in the literature as *Dimroth rearrangement* [33,34].

Table 4 Preparation of ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate: effect of solvent.[a]

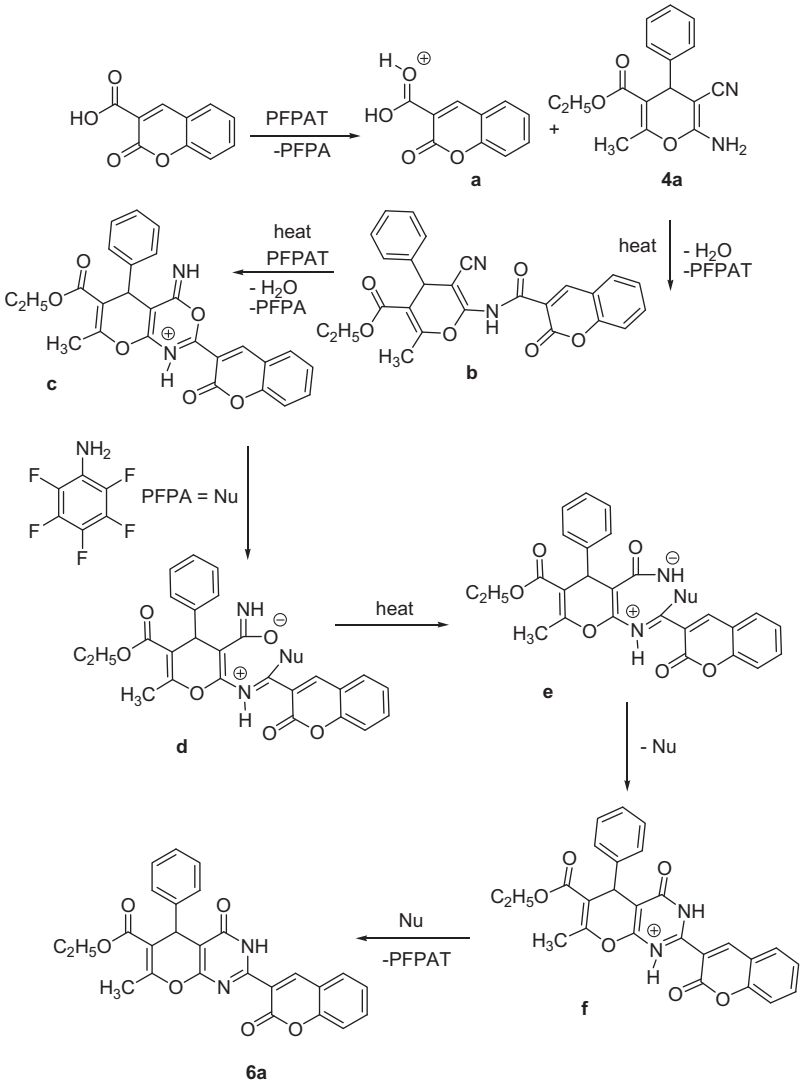
Entry	Solvent	Amount of catalyst (mol%)	Time (h)	Yield (%)[b]
1	1,4-Dioxane	5.0	6.0	66
2	Ethanol	5.0	6.0	82
3	Acetonitrile	5.0	8.0	20
4	THF	5.0	8.0	25
5	Methanol	5.0	6.0	78
6	*t*-BuOH	5.0	6.0	25
7	None	5.0	6.0	89

[a] Reaction conditions: **4a** (1 mmol) and coumarin-3-carboxylic acid (1 mmol) in the presence of PFPAT (5 mol%); 80 °C.
[b] Isolated yields.

Table 5 Preparation of various ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate derivatives.[a]

Entry	R1	Product	Time (h)	Yield (%)[b]	Mp (°C)
1	H	**6a**	6.0	89 (87, 85, 84)[c]	272–274
2	3-OH	**6b**	6.0	85	234–236
3	3-NO_2	**6c**	6.0	84	268–270
4	4-$N(CH_3)_2$	**6d**	5.5	82	280–282
5	4-Cl	**6e**	5.5	87	218–220
6	4-F	**6f**	5.5	86	286–288
7	4-OCH_3	**6g**	7.0	84	220–222
8	4-NO_2	**6h**	5.0	86	266–268
9	4-Br	**6i**	5.5	87	244–246
10	4-CH_3	**6j**	6.0	85	234–236

[a] Reaction conditions: **4a**–**j** (1 mmol) and coumarin-3-carboxylic acid (1 mmol) in the presence of PFPAT (5 mol%) at 80 °C.
[b] Isolated yield.
[c] Reusability of catalyst.



Scheme 3 Proposed mechanism for the formation of **6a**.

Table 6 *In vitro* antibacterial activity of compounds **6a–j**.

Compounds	MIC in μg/mL and zone of inhibition in mm			
	E. coli	*P. aeruginosa*	*K. pneumonia*	*S. aureus*
6a	12.5(15–18)	12.5(15–18)	12.5(15–18)	12.5(16–18)
6b	6.25(16–19)	6.25(19–21)	6.25(15–18)	6.25(16–18)
6c	12.5(14–17)	12.5(15–18)	12.5(15–18)	12.5(16–18)
6d	12.5(12–15)	12.5(12–15)	12.5(15–18)	12.5(15–18)
6e	6.25(16–18)	6.25(15–18)	6.25(15–18)	6.25(16–18)
6f	6.25(16–18)	6.25(15–18)	6.25(15–18)	6.25(16–18)
6g	25(8–11)	25(9–12)	25(8–11)	25(9–12)
6h	25(8–11)	25(9–12)	25(8–11)	25(9–12)
6i	6.25(18–20)	6.25(16–18)	6.25(16–18)	6.25(16–18)
6j	6.25(18–20)	6.25(15–18)	6.25(16–18)	6.25(18–20)
Ciprofloxacin	6.25(30–35)	6.25(26–32)	6.25(21–25)	6.25(25–28)

Biological evaluations

All the compounds were screened for their antibacterial and antifungal activity. Compounds **6a–j** with various substituents in the aromatic ring will be useful in understanding the influence of steric and electronic effects on the biological activity.

Antibacterial activity

The newly synthesized compounds were screened for their *in vitro* antibacterial activity against *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Klebsiella pneumonia* (*K. pneumonia*), and *Staphylococcus aureus* (*S. aureus*) bacterial stains by serial plate dilution method. Serial dilutions of the drug in Muller Hinton broth were taken in tubes, and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth.

A number of antibacterial disks were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted, and plates were dried by placing in an incubator at 37 °C for an hour. Using a punch, wells were made on these seeds agar plates, and minimum inhibitory concentrations of the test compounds in dimethyl sulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as a solvent. The Petri dishes were prepared in triplicate and maintained a 37 °C for 3–4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ciprofloxacin as standard. Zone of inhibition was determined for **6a–j**. The results are summarized in Table 6. The MIC values were evaluated at concentration range, 6.25–25 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm. From the activity report (Table 6) it was notified that most of the compounds showed moderate activity against all the bacterial strains.

Antifungal activity

Newly prepared compounds were also screened for their antifungal activity against *Aspergillus flavus* (*A. flavus*), *Rhizopus schipperae* (*R. schipperae*), *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*) in DMSO by serial plate dilution method. Sabourauds agar media were prepared by dissolving peptone (1 g). D glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the *pH* to 5.7. Normal saline was used to make a suspension of sore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted, and plates were dried by placing in an incubator at 37 °C for 1 h. Using a punch, wells were

Table 7 *In vitro* antifungal activity of compounds **6a–j**.

Compounds	MIC in μg/mL and zone of inhibition in mm			
	A. flavus	*R. schipperae*	*A. niger*	*C. albicans*
6a	12.5(16–20)	12.5(18–22)	12.5(20–22)	12.5(20–22)
6b	6.25(16–20)	6.25(18–22)	6.25(20–22)	6.25(18–20)
6c	12.5(15–18)	12.5(18–22)	12.5(20–22)	12.5(18–20)
6d	12.5(10–12)	12.5(12–16)	12.5(16–18)	12.5(18–18)
6e	6.25(12–16)	6.25(12–16)	6.25(16–18)	6.25(16–18)
6f	6.25(10–14)	6.25(12–14)	6.25(12–15)	6.25(14–16)
6g	25(10–12)	25(8–11)	25(10–12)	25(10–12)
6h	25(10–12)	25(9–12)	25(10–12)	25(10–12)
6i	6.25(15–16)	6.25(18–22)	6.25(18–22)	6.25(18–20)
6j	6.25(14–18)	6.25(16–14)	6.25(16–18)	6.25(16–18)
Amphoterecin-B	6.25(22–26)	6.25(30–34)	6.25(27–30)	6.25(28–32)

made on these seeded agar plates. Minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with Amphoterecin-B as standard. Zones of inhibition were determined for **6a**–**j**. The results are summarized in Table 7. The MIC values were evaluated at concentration range, 6.25–25 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm. All the newly synthesized compounds showed moderate activity against all the fungal strains.

Conclusions

Various derivatives of ethyl 4,5-dihydro-7-methyl-4-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-pyrano[2,3-d] pyrimidine-6-carboxylate (**6a**–**j**) were synthesized from the reaction of 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylates (**4a**–**j**) with coumarin-3-carboxylic acid in the presence of PFPAT as reusable and inexpensive Brønsted acidic catalyst under solvent-free condition. All the synthesized compounds were screened for their *in vitro* antimicrobial activity. The newly synthesized compounds showed moderate activity against all the bacterial and fungal strains.

Conflict of interest

The authors have declared no conflict of interest.

Acknowledgements

The authors Mansoor and Aswin are thankful to the Management of C. Abdul Hakeem College, Melvisharam 632 509 (TN), India for the facilities and support.

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